Medical and Pediatric Oncology 27:422–428 (1996)

Histological Analysis of Aggressiveness and Responsiveness in Wilms' Tumor

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The clinical behavior and outcome for any neoplasm are determined originally by its aggressiveness. As adjuvant therapy becomes increasingly effective for that neoplasm, responsiveness to therapy assumes a larger role in determining outcome. Wilms' tumor (WT) provides instructive examples of the dissociation of aggressiveness from responsiveness. The presence of gigantic nuclei with multipolar mitotic figures (anaplasia) appears to be a marker of resistance to therapy, but not of increased aggressiveness. For this reason, anaplasia in a stage I WT and anaplasia confined to discrete foci within the primary tumor have no adverse prognostic significance following surgical resection. The prognostic significance of anaplasia is apparently limited to those patients in whom anaplastic cells remain following attempted surgical resection.

WT with predominantly epithelial differentiation usually have a low degree of aggressiveness. In this study, 81.3% of WT with this pattern were stage I. This feature accounts for the high cure rate associated with this pattern prior to the advent of effective adjuvant therapy. However, epithelial predominant WT that present with advanced stage disease may be quite resistant to therapy, with relapse and death rates higher than for more aggressive WT patterns. In contrast, the diffuse blastemal pattern is associated with marked aggressiveness, but with high survival rates suggesting it is usually responsive to current therapy. These features illustrate the independence of aggressiveness and responsiveness in determining outcome for some patients with cancer. Grading systems must be reevaluated with each significant change in therapy. In order to formulate rational therapy, it is important to determine whether prognostic markers are associated with aggressiveness or responsiveness.

Key words: Wilms' tumor, nephroblastoma, tumor grading, prognostic markers, anaplasia, tumor biology, tumor histology

INTRODUCTION

Prior to the modern era of cancer therapy, the cancer cell existed in a "state of nature," where its aggressiveness determined its clinical behavior and outcome. The principal manifestations of tumor aggressiveness are invasiveness and the capacity for metastatic spread. Growth rate is an independent variable not necessarily linked to aggressiveness, but which does influence the rate of progression of aggressive lesions. Since aggressiveness is the primary determinant of surgical resectability for most neoplasms, tumors of relatively low aggressiveness tended to yield the highest survival rates in the era prior to effective adjuvant therapy.

In today's therapeutic milieu, the cancer cell faces a new and rapidly changing environment consisting of increasingly effective treatment modalities. As the effectiveness of adjuvant therapy increases, the importance of aggressiveness is diminished, and responsiveness to therapy becomes an increasingly important determinant of outcome. If an ideal therapeutic approach were available for a given cancer, capable of eradicating every tumor cell without endangering the host, then aggressiveness and surgical resectability would have no impact upon outcome. Figure 1 illustrates diagrammatically the changing relative importance of aggressiveness and responsiveness with increasingly effective adjuvant therapy for a given neoplastic entity.

Prior to the development of effective adjuvant therapy, outcome data for a neoplasm or prognostic marker are direct indicators of aggressiveness, but with increasingly effective therapy these data will be more reflective of responsiveness. Responsiveness to therapy is usually agent specific. Relapse and survival data generated in one therapeutic epoch may therefore be irrelevant and misleading when applied in another epoch. Features defining degree of malignancy or grade for a given neoplasm can vary over time, and must be continuously reviewed when new therapies are introduced. Prognostic determi-

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Received May 25, 1995; accepted February 6, 1996.

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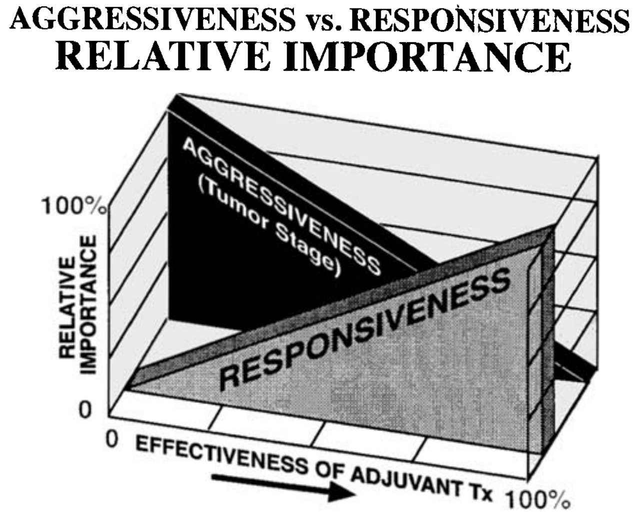

Fig. 1. The changing relative impact of aggressiveness and responsiveness upon survival with increasing effectiveness of adjuvant therapy.

nants and grading schemes that were powerful in one therapeutic epoch may be invalid in another. It is important to know whether a grading scheme or prognostic marker reflects aggressiveness, responsiveness, or both. A marker of resistance to a specific therapy, for example, might have no prognostic relevance when the tumor has been completely resected, or when another therapeutic agent is employed.

Wilms' tumor (WT) is an instructive model for investigating cytohistological correlates of aggressiveness and responsiveness in cancer cells. WT are histologically heterogeneous, with a kaleidoscopic spectrum of cell types and degrees of differentiation, and most children with this diagnosis, even those with advanced-stage disease, are curable with modern therapeutic approaches. Of particular importance is the fact that the majority of cases of this uncommon neoplasm are entered on collaborative therapeutic trials, including the National Wilms' Tumor Study (NWTS), which have made possible the centralized pathological review of large cohorts of cases staged, treated, and followed according to standardized protocols [1,2].

This paper reviews the evolution of concepts concerning several histopathological prognostic features of WT, and illustrates how the analysis of tumor aggressiveness and resistance can facilitate the development of rational therapeutic strategies.

ANAPLASIA IN WT: A MARKER OF AGGRESSIVENESS OR UNRESPONSIVENESS?

Anaplasia in WT refers to the presence of gigantic, irregularly shaped nuclei with multipolar mitotic figures [3,4]. This feature, present in 5% of WT specimens, is a powerful marker of adverse prognosis, and is currently the only criteron for histopathological grading of WT used by the NWTS. WT with anaplastic nuclear changes are placed in the unfavorable histology (UH) category, and the remaining 95% are designated as having favorable histology (FH).

The observation that anaplastic nuclear changes in WT were associated with high relapse and death rates was made during retrospective histological analysis of cases entered on the first NWTS (NWTS-1, 1969-1974) [3]. This finding was reported in 1978, when NWTS-2 (1974–1979) was nearing its conclusion. Patients on the first two NWTS trials were therefore treated according to stage alone, without regard for the presence or absence of anaplasia. The design of NWTS-3 (1979–1986) included intensified therapy for anaplastic WT of all stages [5]. Anaplastic WT of all stages were treated with radiotherapy and were randomized to receive chemotherapy for 15 months, consisting of regimen DD (dactinomycin, vincristine, doxorubicin) or regimen J (same agents as DD, plus cyclophosphamide). Thus, the stage was set, serendipitiously, for the analysis of clinical responses of anaplastic WT to therapeutic approaches of differing intensity.

While NWTS-3 was still in progress, a review of anaplastic WT treated on the first two studies was reported [6], with results from multivariate analysis suggesting that patients with localized anaplastic WT fared better than those with disseminated disease. In 1986 it was noted that death rates for stage I anaplastic WT on NWTS-2 had been no higher than for stage I FH cases, suggesting that therapeutic intensification was not necessary for these patients [7].

A detailed review of anaplastic WT entered on NWTS-3 confirmed the generally good outcome for stage I anaplastic WT cases, all of whom had been treated by the intensified protocols noted above [4]. Sixteen of 17 cases in that study (94%) were surviving without relapse, compared to 93% for stage I FH WT on the same study. Review of cases from NWTS-2 revealed that 11 of 12 stage I anaplastic WT treated with conventional therapy were also survivors [4]. The adverse prognosis associated with anaplasia was restricted to patients with stage II-IV disease, worsening with increasing stage. Based on these results, patients entered on NWTS-4 (1986–1995) with stage I anaplastic WT were randomized to receive the same therapy as those with stage I FH WT. Table I summarizes relapse and survival figures for stage I anaplastic WT on the first four NWTS trials. Most patients in this category experienced an excellent outcome regardless of the type of adjuvant therapy employed.

These observations provided the first clue that anaplasia in WT might be a marker of resistance to chemotherapy, but not of increased aggressiveness [4]. Several other findings reinforce the concept that anaplastic nuclear changes in WT are markers of increased resistance to adjuvant therapy, but not of increased aggressiveness: 1) anaplastic WT are neither larger nor much more extensive

TABLE I. Stage I Anaplastic WT (NWTS-1-4)

Study [Ref.]	Therapy	Patients	Relapses (%)	Deaths (%)
NWTS-1 [2]	FH	4	1	1
NWTS-2 [3]	FH	12	1	1[a]
NWTS-3 [3,4]	UH	15	2	2
NWTS-4[b]	FH	24	2	2
Total		55	6 (10.9)	5 (9.3)[c]

[a]Death due to toxicity, no residual tumor present at death.
[b]NWTS Data and Statistical Report, July 1994 (follow-up not yet complete).
[c]Deaths due to tumor. One NWTS-2 case dying from toxicity censored from calculation.

at the time of diagnosis than FH WT [6]; 2) anaplastic cells occur with similar frequency in WT treated prior to nephrectomy as in untreated WT, suggesting that they are not affected by therapy [8]; 3) survival for patients presenting with metastatic anaplastic WT is rare. In a recent report only 1 of 14 randomized NWTS-3 and NWTS-4 patients presenting with stage IV diffusely anaplastic WT survived [9].

Focal vs. Diffuse Anaplasia

If the adverse prognosis associated with anaplastic nuclear changes in WT is primarily a reflection of increased resistance to current therapy, then the distribution of anaplasia within the tumor becomes critically important. A child with disseminated WT, but with anaplasia confined to a discrete focus within the resected primary tumor, might have an outcome similar to that for nonanaplastic WT of the same stage. This led us to reconsider the original definition of focal vs. diffuse anaplasia proposed in the 1978 NWTS report [3]. That definition had been designed to address the question of whether tumors with scanty anaplastic cells fared better than those with larger numbers of such cells. We arbitrarily chose 10% of microscopic fields as the dividing line between focal anaplasia (FA) and diffuse anaplasia (DA), regardless of location or distribution of anaplastic cells within the tumor. The presence of anaplastic changes in an extrarenal site or metastatic deposit would qualify for the designation of FA if most microscopic fields from the primary tumor were free of anaplastic changes. A WT with anaplasia sparsely distributed throughout the entire tumor could also meet the original definition of FA. Though patients with FA tended to fare somewhat better than those with DA, this difference did not attain statistical significance on NWTS-1, NWTS-2, or NWTS-3 [3–6]. For this reason, patients with FA and DA WT were treated identically on NWTS-3 and NWTS-4.

The hypothesis that the topographical distribution of anaplasia might be a critical determinant of prognosis led us to propose and test a revised definition of FA, based upon the distribution of anaplasia within the tumor without respect for the relative proportion of anaplastic nuclei. To qualify for the revised definition of FA, anaplastic changes had to be confined to one or more clearly defined regions within the primary tumor, and absent from extrarenal tumor extensions or metastatic deposits [9–11].

This revised definition proved to have remarkable prognostic significance. In a review of cases entered on NWTS-3 and 4, relapse and survival figures for FA cases of all stages were similar to those for FH WT cases [9–11]. The poor outcome associated with stage II-IV anaplastic WT was largely confined to cases in the DA category. The prognostic significance of this revised definition was shown most clearly by the outcomes for cases presenting with stage IV disease. Among eight cases presenting with stage IV tumor, and FA in the primary tumor, there were no deaths. Only one of 23 cases (4.7%) survived who had stage IV disease and DA in the primary lesion [10]. This excellent outcome for stage IV FA cases implies that the metastatic deposits in these cases tend to be composed of cells responsive to adjuvant therapy. Cases with DA in the primary tumor were more likely to have metastases composed of resistant cells.

These results suggest that anaplastic cells arise clonally within a WT, and expand over time to become distributed more generally throughout the lesion. FA, using the new definition, apparently identifies an early stage in this process of tumor progression.

The primary determinant of outcome for anaplastic WT seems to be the completeness of surgical removal of resistant tumor cells. The mere presence of anaplastic cells in a tumor does not confer a worse prognosis if the entire tumor, or the entire anaplastic focus, has been removed. Patients who have stage I anaplastic WT, or focally anaplastic WT of any stage (using the revised definition), can be spared the toxic effects of therapeutic intensification and have the same high likelihood of survival associated with FH WT. This illustrates the clinical importance of clearly distinguishing between aggressiveness and responsiveness in dealing with a prognostic marker. Overly simplistic concepts of unfavorable or favorable for a tumor pattern or marker can lead to inappropriate therapy and prognosis, unless the precise meaning of that term is established for each neoplastic entity or prognostic criterion.

AGGRESSIVENESS AND RESPONSIVENESS IN NONANAPLASTIC WT

Pathologists have long been intrigued by the possibility that the extraordinary histological diversity within the WT spectrum might have prognostic relevance. Several reports published during the 1950s through the 1970s indicated that WT composed predominantly of differentiated epithelial structures were associated with a relatively good prognosis when compared to all other patterns [12–16]. Table II summarizes some of the most important early reports concerning this observation, and Chatten's

TABLE II. WT With Predominant Epithelial Differentiation

Author [Ref]	Results	
Williams, 1958 [12]	"Tumours with a high proportion of differentiated tubules and those with a papillary appearance are more common in younger infants and appear to carry a better prognosis"	
Bodian and Rigby, 1964 [13]	12/89 cases (13.5%) 1925–1962 9/12 (75%) survived Other patterns: 17/77 (22%) survived	6 < 1 year at diagnosis
Lawler et al., 1975 [14]	6/67 cases (9%) 1954–1969 5/6 (83%) survived Other patterns: 18/61 (29.5%) survived	Median age 3 years
Chatten, 1976 [15]	9/95 cases (9.5%) 1939–1972 9 (100%) survived Classic patterns: 33/59 (55.9%) survived	7 < 1 year at diagnosis
Chambers et al., 1978 [16]	6/47 cases (12%) 1949–1976 6 (100%) survived Other patterns: 14/34 (41%) survived	4 < 2 years at diagnosis

scholarly review is recommended for a detailed analysis of the literature up to 1976 [15]. Survival rates for epithelial predominant WT were remarkably better than for all other patterns combined. Several authors also noted that this pattern was associated with relatively young age at diagnosis. It is important to note that most patients in these early retrospective reviews had been treated prior to the era when therapy with dactinomycin and vincristine together had become standard for most WT patients.

The better outcome for epithelial predominant WT noted in early reports has become less apparent in recent decades, due to markedly improved survival rates for nonanaplastic WT in general. In our review of cases entered on NWTS-1 [3], epithelial predominant patterns were associated with generally excellent outcomes, but these did not differ significantly from the other nonanaplastic histological patterns analyzed. Therefore, the earlier observation that epithelial differentiation may be a marker of particularly good prognosis in WT has been widely ignored in recent decades, though a few authors have continued to emphasize the good prognosis associated with this pattern [17].

Despite the lack of apparent prognostic significance associated with pattern in nonanaplastic WT in the modern era, we have continued to record the histological pattern of all cases reviewed in the NWTS Pathology Center, using the criteria employed in our 1978 study [3]. Tumors where one cell type or pattern comprises at least two thirds of the tumor area in the slide sample are given a pattern designation reflecting the predominant element. Those where no single element comprises at least two thirds of the tumor area are designated as "mixed."

Since anaplastic WT had proven so instructive an example of the dissociation of aggressiveness and responsiveness, we were stimulated to reopen the question of whether histological patterns in FH WT might possess distinctive biological characteristics. Simple outcome figures can be misleading because tumor aggressiveness and responsiveness can influence results in opposite directions. However, the analysis of these features can be facilitated by evaluation of stage distribution and stage-specific relapse and survival rates for the various histological subtypes under investigation. The stage at presentation for a given subtype or pattern should reflect tumor aggressiveness. Those of low aggressiveness should be skewed toward early stage at presentation, and conversely. Survival figures for advanced-stage disease and for relapsed or persistent tumor are most likely to reflect tumor responsiveness, since these are the cases where survival is most directly attributable to responsiveness to therapy.

All cases with unilateral FH WT entered on NWTS-4, treated initially by nephrectomy with adequate histological material reviewed by the NWTS Pathology Center, were included in this analysis. Histological pattern designations for all cases were assigned at the time of initial case review by J.B.B. Thirty-one patients were excluded from the outcome analysis for the following reasons: 23 were lost to follow-up, 7 deaths were due to causes other than persistence or relapse of the original WT, and 1 patient had first relapse to the contralateral kidney.

Table III summarizes the stage distribution among FH WT of selected histological patterns. The most striking results are emphasized by italic type. Tumors composed predominantly of differentiated cell types, either stromal or epithelial, showed a strong tendency toward low stage at presentation. This is most apparent for epithelial predominant WT, of which 81.3% were stage I at diagnosis and only 5.7% were stage III and IV. This implies that epithelial predominant patterns in FH WT are usually of very low aggressiveness. The preponderance of low-stage lesions provides a logical explanation for the distinctly better outcome associated with this pattern in early studies. Since most epithelial predominant WT are likely to be surgically resectable, it is not suprising that they would have fared relatively well prior to the advent of effective

TABLE III. Histological Pattern Vs. Stage Distribution (2,077 Unilateral FH WT, NWTS-4)

	Stage distribution (%)				
Pattern	I	II	III	IV	No.
Mixed	37.3	30.8	21.3	10.6	1,178
Epithelial differentiation	*81.3*	*13.0*	*1.6*	*4.1*	*123*
Epithelial undifferentiation	55.6	11.1	22.2	11.1	63
Stromal differentiation	65.7	14.3	14.3	5.7	35
Diffuse blastema	*4.4*	*19.3*	*46.6*	*29.7*	*249*
Other blastema	31.9	27.7	24.5	15.8	429

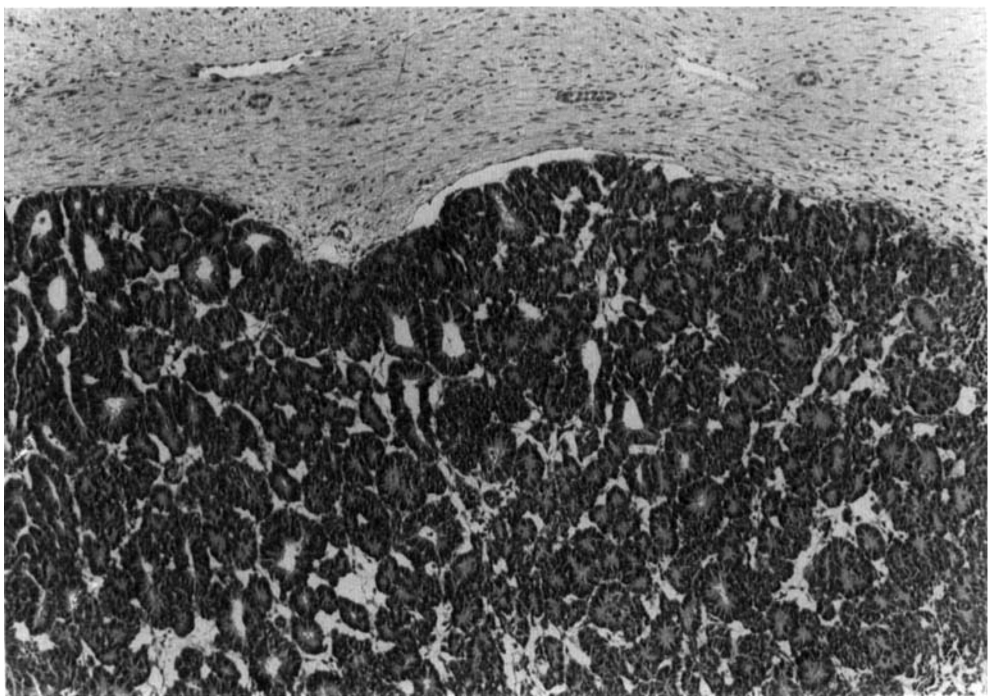

Fig. 2. Epithelial predominant WT showing sharp tumor margin usually seen with this pattern.

chemotherapy. The introduction of effective adjuvant therapy has obscured this distinctive biological feature by producing survival rates for other patterns that are similar to those for the epithelial predominant WT.

A strikingly different stage distribution was observed for another FH WT pattern, which we termed "diffuse blastemal," as shown in Table III. Only 4.4% of WT predominantly composed of this pattern were stage I, and 76.3% were stage III or IV at presentation. The shift toward high stage at presentation indicates that this is a pattern associated with exceptional aggressiveness. The diffuse blastemal pattern is characterized by sheets of blastemal cells lacking organoid aggregation patterns, and by extremely invasive margins. Figures 2 and 3 contrast the margins of a typical tubular predominant WT with those of a WT of the diffuse blastemal pattern. In the era before effective chemotherapy for WT was available, this pattern was associated with extremely poor survival. For example, Bodian and Rigby [13] reported 24 deaths among 26 patients with their pattern G, which corresponded to our diffuse blastemal pattern. In contrast, among 12 patients with their pattern B, corresponding to our epithelial predominant pattern, only 3 died.

The stage at presentation suggested a striking difference in aggressiveness between the differentiated epithelial and diffuse blastemal pattern of WT, both patterns associated with similarly high survival rates in the era of modern chemotherapy. This prompted an investigation of the responsiveness of these two patterns to current therapeutic protocols. The outcome for patients presenting with advanced-stage disease provides direct information concerning responsiveness to current therapy. Table IV compares 4-year relapse and survival results for the epithelial predominant and diffuse blastemal patterns in patients with low vs. high-stage tumors. The small number of stage III-IV epithelial predominant tumors limits this analysis, but the results suggest a better outcome with advanced-stage diffuse blastemal WT than

TABLE IV. Relapse and Survival Results by Histological Pattern and Stage (NWTS-4)

	Relapse-free (%)		Survival (%)	
	2 Year	4 Year	2 Year	4 Year
Stages I/II				
Diffuse blastemal (57)	94.5	83.5	97.8	97.8
Epithelial differentiation (108)	93.6	92.2	99.0	97.6
	$P = 0.50$		$P = 0.93$	
Stages III/IV				
Diffuse blastemal (176)	80.7	79.0	88.9	81.5
Epithelial differentiation (7)	42.9	21.4	100	44.0
	$P = 0.001$		$P = 0.06$	

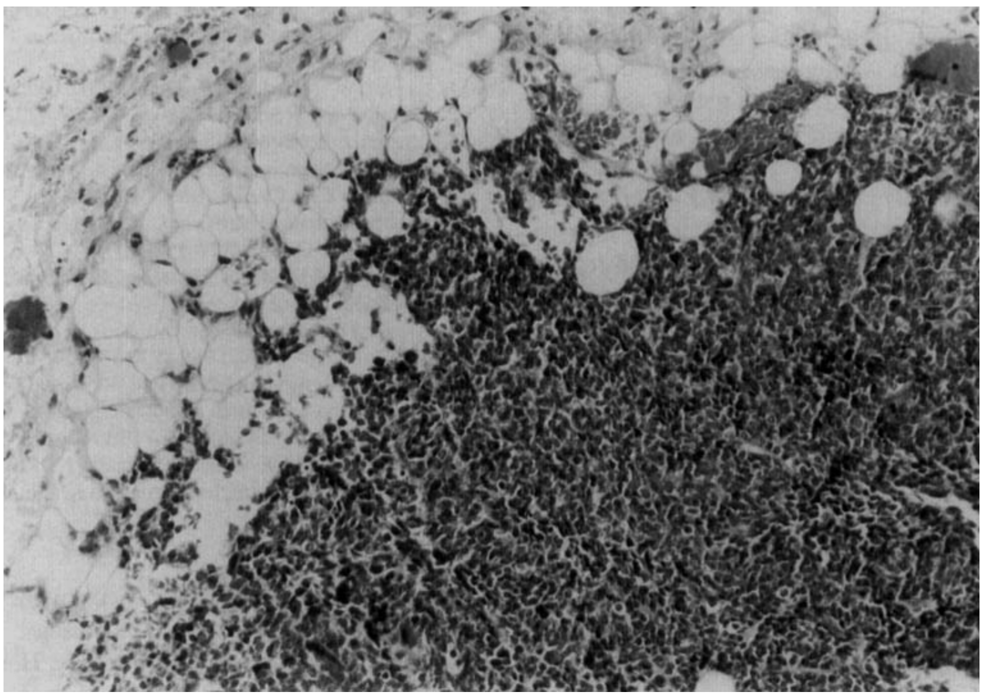

Fig. 3. Diffuse blastemal WT showing aggressive invasion of perirenal fat by sheets of tumor cells.

with advanced-stage epithelial predominant tumors. This seemingly surprising result would imply that the diffuse blastemal pattern, though much more aggressive than the epithelial predominant pattern, is more responsive to chemotherapy. A patient presenting with advanced-stage epithelial predominant WT might require more intensive therapy than required for other more aggressive patterns.

Another biological difference associated with these two patterns is the age at diagnosis, as noted by earlier authors and summarized in Table II. WT with epithelial predominance had a median age at presentation of 17 months, compared to 57 months for those with the diffuse blastemal pattern.

COMMENTS

The examples discussed above illustrate that aggressiveness and responsiveness can influence outcome in different directions in the same tumor. A given cell type or tumor pattern may possess low aggressiveness but be very resistant to current therapy, while a highly aggressive lesion can prove extremely responsive to therapy. It is essential to know whether a marker of good or bad prognosis is associated with aggressiveness, responsiveness, or both. The example of anaplastic WT illustrates how a term such as "unfavorable histology" can be misleading if that pattern is associated primarily with resistance to

therapy. Its adverse prognostic significance is relevant only to the patient with residual tumor. Conversely, a marker of especially favorable prognosis, such as the WT with abundant tubular differentiation, may be equally misleading for the patient who happens to have a more advanced-stage tumor at diagnosis.

Many other patterns observed in WT have potential significance with respect to both aggressiveness and responsiveness. For example, the category designated as differentiated stromal in Table III is associated with a stage distribution quite similar to that for the epithelial differentiated pattern, and many of the same principles may apply. The term "fetal rhabdomyomatous nephroblastoma," coined by Wigger [18] for WT composed predominantly of skeletal muscle, is one of the patterns subsumed under our differentiated stromal predominant category. This pattern is often associated with localized tumor at diagnosis, and with young patient age [18–20]. It can also be associated with poor responses to adjuvant therapy [20]. The relationship between young age at diagnosis and degree of differentiation in WT deserves further exploration. The aggressive blastemal patterns are associated with older age at diagnosis, and may well represent a promotional event within a WT of originally less aggressive pattern.

ACKNOWLEDGMENTS

Supported in part by United States Public Health Service grants CA 42326 and CA 60114.

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COMMENTARY

J. Bruce Beckwith et al. excel in their analytic and critical study of the dynamics of disease and the appropriate descriptive medical technology. Here, they help us reflect on and, as a consequence, better distinguish two extremely important terms used regularly in oncology, i.e., "aggressiveness" and "responsiveness" to therapy. Aggressive tumors (invasive and with the capacity to metastasize) may or may not be responsive to therapy. For example, WT with epithelial differentiation, which usually have a low degree of aggressiveness, had been associated with high cure rates even prior to the advent of effective adjuvant therapy. However, advanced-stage disease with this phenotype can still be resistant to modern therapy. The authors recommend that for the formulation of rational therapy, physicians need to determine whether prognostic markers are associated with aggressiveness or responsiveness. How timely is this advice, now that several investigators are exploring novel prognostic markers, such as the genetic index described by Grundy et al. in this issue.